DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

SEP 29 2004

Rakesh M. Amin, LL.M., R.Ph.
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217 North Jefferson Street, Fifth Floor
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Dear Mr. Amin:

This is to inform you that the notification you submitted, dated July 19, 2004, on behalf of your client, Ztis, Inc., pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) was filed by the Food and Drug Administration (FDA) on July 26, 2004. Your notification concerns the substance called "*Clematis mandshurica* extract" an extract of the botanical "*Clematis mandshurica* Rupr." that you intend to market as a new dietary ingredient.

The notification describes the to be marketed product as SKI306X, marketed in Korea and Australia as JOINS® tablet and Carathron®, respectively, which is a purified extract from a mixture of three oriental herbal medicines. The notification informs FDA that Ztis, Inc. "intends to market SKI306X (JOINS®) in 200 mg tablets containing about 100 mg of "*Clematis mandshurica*" extract". The notification further states that "the conditions of use suggested on the labeling are: as a dietary supplement to support healthy joints and cartilage, take one tablet, 2-3 times daily."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing "*Clematis mandshurica* extract" will reasonably be expected to be safe.

Your notification fails to clearly identify the composition and manufacturing process for the new dietary ingredient "*Clematis mandshurica* extract" or the dietary supplement SKI306X that contains it. Further, according to the notification, the dietary supplement that contains the new dietary ingredient also contains extracts of two other botanicals, namely, *Trichosanthes kirilowii* and *Prunella vulgaris*. The notification contains no information on the history of use, identity, or safety of extracts of these two ingredients when used alone or in combination with an extract of *Clematis mandshurica*. Moreover, the composition and weight of the dietary supplement SKI306X is unclear. For example, the description on page 18 of the notification states that SKI306X tablets weight 430 mg and contain 25% "*Clematis mandshurica* extract", whereas on page 4 of the notification, the amount of "*Clematis mandshurica* extract" in 200 mg tablets should be 50%.

It is also unclear whether the test substances used in the referenced studies that are cited as evidence supporting the safety of SKI306X are the same as the *Clematis mandshurica* extract-containing product that is the subject of the notification. The relationships between SKI306X and the products JOINS® and Carathron® are not described. Therefore, it is not clear whether the test substances used in the various referenced studies are qualitatively and quantitatively similar to SKI306X or how these studies are relevant to evaluating the safe use of your dietary supplement that contains the new dietary ingredient "*Clematis mandshurica* extract" under its recommended conditions of use.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "*Clematis mandshurica* extract", when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of July 26, 2004. After the 90-day date, the notification will be placed on public display at FDA's Division of Docket Management in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Linda Pellicore, Ph.D., at (301) 436-2375.

Sincerely yours,

Susan J. Walker, M.D.
Director
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